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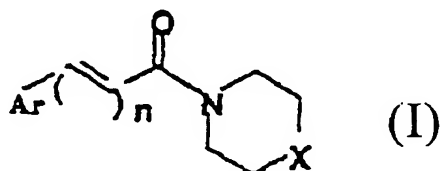
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(54) Title: **SUBSTITUTED ARYL ALKENOIC ACID HETEROCYCLIC AMIDES POSSESSING PUNGENT TASTE**

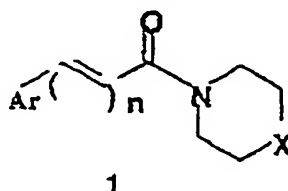


(57) Abstract: The present invention relates to novel compounds possessing specific hot, pungent and spicy taste when subjected to direct pungency evaluation, which may be useful as food additives and anti-oxidants, however the said compounds do not add to any nutritional value but the synthesized compounds can possess useful pharmacological properties which is expected to find application in new test models for the development of anti-inflammatory drugs, bioavailability enhancers and for the study of hepatic drug metabolising mechanism; also relates to a process for preparing the said compounds Formula.

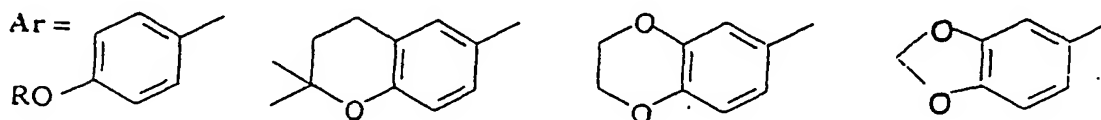
Novel substituted aryl alkenoic acid heterocyclic amides

Field of the invention

- 5 The present invention relates to novel substituted aryl alkenoic acid heterocyclic amides. The invention particularly relates to the novel substituted aryl alkenoic acid heterocyclic amides of general formula 1, useful as food additives and in pharmaceutical applications:



- 10 wherein $n = 1$ or 2 , $X = O$ or $N-CH_3$ and



wherein $R =$ linear or branched C_1 to C_5 alkyl chain

15 Background of the invention

- Aroma, flavour and taste are considered to be the three important parameters for determining the quality of spices or condiments. The aroma and flavour of a spice depends upon the presence of volatile components, which are perceived through the olfactory epithelium present in the nose. The olfactory substances are primarily mono-, sesqui- or diterpenes, low molecular weight hydrocarbons, heteroacyclic or heterocyclic compounds. The taste is perceived by the taste buds present on the surface of the tongue. The interactions between the pungent molecules and receptors present on the surface of the tongue are the main cause of generation of hot sensation or thermogenecity which is associated with pungency. More pungent the substance, more is the duration of the feeling of hotness. This feeling of hotness may also be perceived on other tender parts of the skin. Most of the known natural pungent substances are aromatic in nature. Some of the most commonly known natural pungent substances include piperamides such as piperine from black pepper (*Piper nigrum*), capsaicinoids such as capsaicin and dihydro-capsaicin from red chillies (*Capsicum annum*) and gingeroids like gingerol from ginger (*Zingiber officianalis*) etc. The chemistry and properties of pungent compounds from natural sources
- 30

has recently been reviewed (Nakatani, Nobugi; Koryo, 1995, 185, p 59-64, *Chem. Abs.* 123, 5520 n).

These pungent principles which possess anti-oxidant properties are also associated with many physiological actions viz piperamides, capsaicinoids as well as gingeroids are reported to possess anti- inflammatory properties (Lewis,D. A. in Anti- inflammatory drugs from plant and marine sources; *Birkhauser Verlag*, Berlin, 1989, p 216-220; Janusz, J.M., *J. Med. Chem.* 1993,36, p 2595). Both piperine and dihydrocapsaicin were found to interact irreversibly with hepatic drug metabolizing enzymes thereby inhibiting their activity as indicated by prolongation of pentobarbital sleeping time in rats (SushYoung- Joon, A, et al., *Life sciences*, 1995, 56(16), p 305-31 1; Atal, C. K. et al., *J. Pharmacol. Exp. Therp.* 1985, 232, p 258-262).

Only few reports have appeared in the literature related to the evaluation of structure with respect to pungency. Wilbur Scoville developed direct subjective method of analysis of capsaicin and related extracts for their pungency evaluation in 1912. In this method potency of pepper was measured as heat units by diluting the extracts until pungency was just detected after placing a drop on the tongue. Pure capsaicin was thus assigned 10^7 units and jalapeno 10^3 units (Scoville, W. J., *Am. Pharm. Assoc.* 1912, 1, p 453-454). Indirect evaluations of pungency through the measurement of physiological effects have also been employed. For example Watnabe et al. reported the assessment of pungency related thermogenecity to structure of capsaicin analogues by correlating it with adrenal catecholamine secretion in rats (Watnabe, Tatsno et al. *Life. Sci.* , 1994, 54(5), p 369-374; *Chem. Abs*, 120: 94792f). Astringent and pungent substances were studied using a multichannel taste sensor by observing the changes in electric potential in lipid membranes. However pungent substances were found to have no effect on the membrane potentials (Iiyama, Satoru et al., *Chem. Senses*, 1994, 19(1), p 87-96; *Chem. Abs.* 120: 295156).

Known natural or synthetic pungent substances are invariably oxygenated aromatic compounds with an alkyl side chain and a heteroatom comprising preferably an amide linkage in the side chain. Some of these compounds were found to possess hot pungent characteristics on preliminary evaluation. On the basis of above observation several new series of aryl alkenoic acid amides were synthesised and their structure and pungency relationship has also been established. Another important aspect of the development of these compounds is the possibility of their utilisation as new test models for the study and

management of the phenomenon of pain and inflammation. These observations are based on the recent work carried out by the David Julius et al. who have identified the capsaicin receptor by isolating the complimentary DNA encoding the binding protein (Julius, D. et al. *Nature*, 1997, 389, p 816-824). Isolation and identification of the receptor protein is an
5 important development for the study of new pharmacological targets which will help in understanding the phenomenon of chronic pain caused by arthritis, spinal cord injury or diabetic neuropathy. It is expected that vanilloid receptor and the receptor for the synthesised compounds of general formula 1 may turn out to be the same. Therefore, the development of these novel compounds may provide a diverse and effective alternate to
10 capsaicin and related vanilloids.

Objects of the invention

The main object of the present invention is to provide the novel substituted aryl alkenoic acid heterocyclic amides.

Another object of the present invention is to provide an economical and effective process for
15 the preparation of aryl alkenoic acid heterocyclic amides of general formula I.

Still another object of the present invention is to provide novel synthetic compounds useful as thermogenic, pungent and spicy agents.

Yet another object of the present invention is to provide novel compounds which can find application as new test models for the development of anti-inflammatory drugs,
20 bioavailability enhancers and for the study of hepatic drug metabolising mechanism.

Still yet another object of the invention is to provide novel aryl alkenoic acid heterocyclic amides of general formula 1 which may be useful as hot, pungent and spicy agents, and also as food additives, anti-oxidants, bioavailability enhancers and for the study of hepatic drug metabolising mechanism including UDP- glucose dehydrogenase and glucuronidation
25 activities.

Summary of the invention

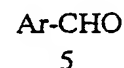
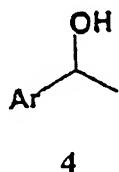
The compounds of this invention are all novel and possess specific hot, pungent and spicy taste when subjected to direct pungency evaluation. The compounds of the present invention do not add to any nutritional value. These compounds may be useful as food additives and
30 anti-oxidants. The synthesised compounds can possess useful pharmacological properties which is expected to find application in new test models for the development of anti-inflammatory drugs, bioavailability enhancers and for the study of hepatic drug metabolising mechanism.

Accordingly, the present invention provides a process for the preparation of novel aryl alkenoic acid heterocyclic amide of general formula 1, wherein n,x,Ar and R have the same definition as mentioned earlier

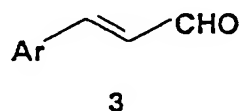
Detailed description of the invention

5 In accordance, the present invention provides a process for the preparation of aryl alkenoic acid heterocyclic amide of general formula 1, useful as food additives and in pharmaceutical applications, said process comprises steps of:

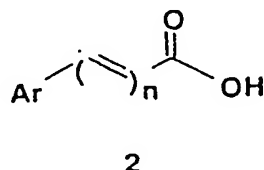
- (a) reacting aldehyde of general formula (5) with alkyl magnesium halide with constant stirring at ambient temperature in an anhydrous ethereal solvent to produce corresponding phenyl ethanol of general formula (4),



- (b) treating the compound of general formula (4) with dimethyl formamide and phosphorous oxychloride at 0° to 10°C for 20-40 hours, working up the reaction mixture by adjusting the pH of the solution and isolating the product of general formula (3) by using conventional method,



- (c) reacting the compound of general formula (3) with witting reagent in presence of a base at a temperature range of 15-80°C in an ethereal solvent for a period of 1-80 hours to get the corresponding carboxylic ester,
- (d) hydrolysing the ester of step (c) with strong alkali solution followed by acidification of the reaction mixture to produce the corresponding carboxylic acid of general formula (2),



(e) reacting compound of step (d) having general formula (2) with thionylchloride in presence of an organic solvent at a temperature range of 70°C-80°C, removing the solvent to obtain the corresponding acid chloride,

5 (f) reacting the acid chloride of step (e) with heterocyclic amine in presence of an inert organic solvent at a temperature range of 0 to 50°C for 1 to 16 hours, isolating the product of general formula 1 by purifying the reaction mixture.

In an embodiment of the present invention, the alkyl magnesium halide used is methyl magnesium iodide.

10

In another embodiment, the ethereal solvent used is selected from group consisting of diethyl ether and tetrahydrofuran and preferably tetrahydrofuran.

In yet another embodiment, the solution of the reaction mixture is adjusted to pH 6 to 8 to
15 isolate the required intermediate product.

In still yet another embodiment, the product after preadjustment of pH is isolated by either filtration or extraction with organic solvent selected from a group consisting of ethylacetate, chloroform, dichloromethane and dichloroethane.

20

In still another embodiment, the witting reagent used is prepared from the reaction of equimolar mixture of triphenyl phosphine and bromomethyl acetate or bromoethylacetate.

In still further embodiment, the alkali used for hydrolysis is selected from the group
25 consisting of sodium hydroxide, potassium hydroxide and calcium hydroxide.

In yet another embodiment, the acidification of the reaction mixture is performed using sulfuric acid or hydrochloric acid.

30 In still another embodiment, the condensation of acid chloride and heterocyclic amine is carried out in an organic solvent selected from the group consisting of benzene, toluene, dichloromethane and ethyl acetate and preferably dichloromethane.

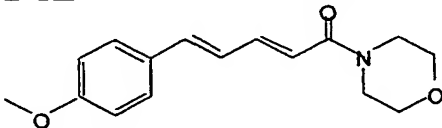
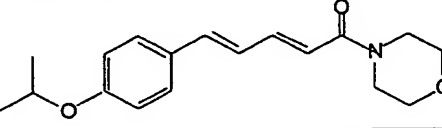
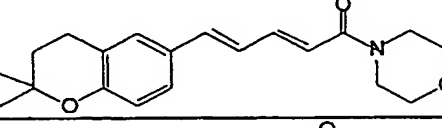
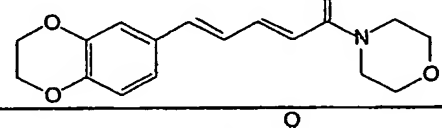
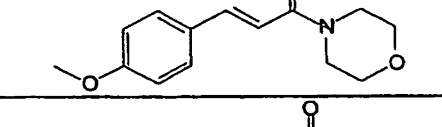
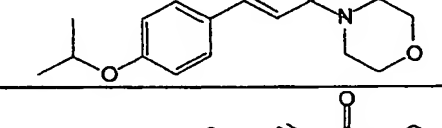
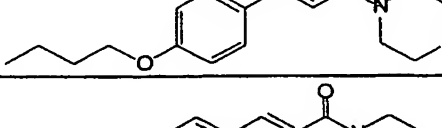
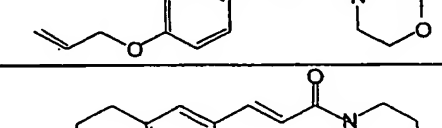
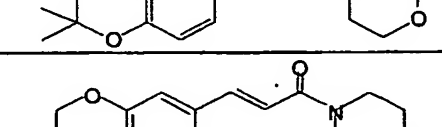
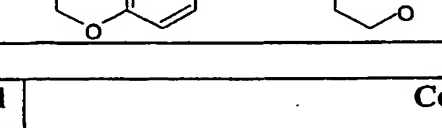
In a further embodiment wherein, purification of the product is carried out by employing
35 crystallization or column chromatography technique.

In yet another embodiment, the novel aryl alkenoic acid amide compounds prepared can be used as best models for the study and management phenomenon of ailments like pain and inflammation.

- 5 In a further embodiment, the novel aryl alkenoic acid amide compounds can be used as best models for the development of inflammatory drugs, bioavailability enhancers and also for the study of hepatic drug metabolic mechanism.

10 The compounds of above invention were assessed in terms of the heat units for ascertaining their potency, by a panel of five untrained volunteers through a subjective or direct analysis using modified W. Scoville method. A stock solution of the compound (1%) in alcohol: water (1:1) was diluted until the sensation of pungency/ hotness just detected by placing 5 μ l of the solution on the tip of the tongue of the volunteers. In all the cases the pungency measurement was made in the reverse order i.e. from less dilute to more dilute solutions till
15 pungency detection was just possible. Mouth and tongue were thoroughly washed with water after each evaluation, sufficient time gap was given before the next evaluation was initiated. In most of the compounds a clear solution was obtained in stock solutions. In some cases where solubility was poor, a uniform suspension was prepared through magnetic stirring or sonication. Although individual perception of pungency varied from person to
20 person, on an average fair consistency was achieved.

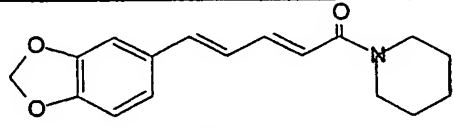
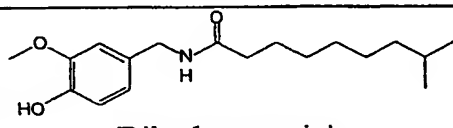
Structure and pungency index of some of the representative compounds of general formula 1

S.No	Structure	M.F.	M.P.°C	Pungency index
i		C ₁₆ H ₁₉ NO ₃	133	10 ⁶
ii		C ₁₈ H ₂₃ NO ₃	134	10 ⁷
iii		C ₂₀ H ₂₅ NO ₃	171	10 ⁴
iv		C ₁₇ H ₁₉ NO ₄	137	10 ⁴
v		C ₁₄ H ₁₇ NO ₃	95	10 ⁵
vi		C ₁₆ H ₂₁ NO ₃	98	10 ⁶
vii		C ₁₈ H ₂₃ NO ₃	117	10 ⁷
viii		C ₁₇ H ₂₃ NO ₃	70	10 ⁴
ix		C ₁₆ H ₁₉ NO ₃	88	10 ⁶
x		C ₁₅ H ₁₇ NO ₄	139	10 ⁴

Compound No.	Compound Name
i)	5- (4 -methoxy phenyl) - 2E, 4E-pentadienoic acid morpholine amide
ii)	5- (4 - isopropyloxy phenyl) - 2E, 4E-pentadienoic acid morpholine amide
iii)	5- (2H)-2,2-dimethyl-3,4-dihydro-benzopyran-6-yl-2E, 4E-pentadienoic acid morpholine amide

iv)	5- (3,4 –ethylenedioxy phenyl) - 2E, 4E-pentadienoic acid morpholine amide
v)	3-(4 –methoxy phenyl)-2E-propenoic acid morpholine amide
vi)	3-(4 –isopropoxy phenyl)-2E- propenoic acid morpholine amide
vii)	3-(4 –butyloxy phenyl)-2E- propenoic acid morpholine amide
viii)	3-(4 –allyloxy phenyl)-2E- propenoic acid morpholine amide
ix)	3-[(2H)-2,2-dimethyl-3,4-dihydro-benzopyran-6yl]-2E-propenoic acid morpholine amide
x)	3 - (3,4 –ethylenedioxy phenyl) – 2E-propenoic acid morpholine amide

Pungency index of reference compounds

A	 Piperine	$C_{17}H_{19}NO_3$	130	10^4
B	 Dihydrocapsaicin	$C_{18}H_{29}NO_3$	—	10^6

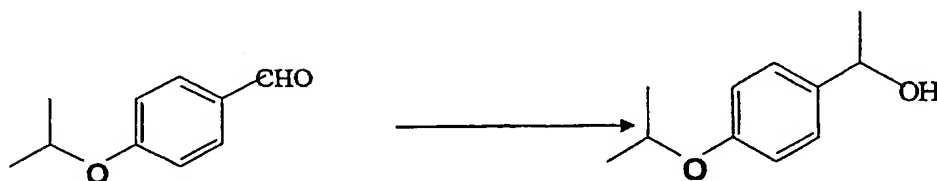
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The invention is illustrated with the following examples, which should not be construed as limiting the scope of the invention.

10 Example-1

Preparation of 5-(4-isopropoxy phenyl)- 2E,4E-pentadienoic acid morpholine amide of formula 1 ($n=2$, $x=O$ and $Ar = 4$ -isopropoxy phenyl

(i) Preparation of 1-(4-isopropoxy phenyl) ethanol of formula 4 ($R = C_3H_7$)



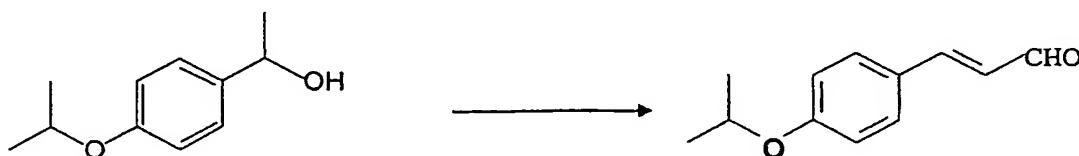
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A solution of 4-isopropoxy benzaldehyde of formula 5 (5g,30 mmol) in dry diethyl ether is slowly added to an ethereal solution of Grignard reagent prepared from magnesium metal (0.84g, 35 mmol) and iodomethane (2.6 ml, 40 mmol) and the contents stirred for 1 hour at room temperature. After the completion of the reaction, the mixture is worked up by adding

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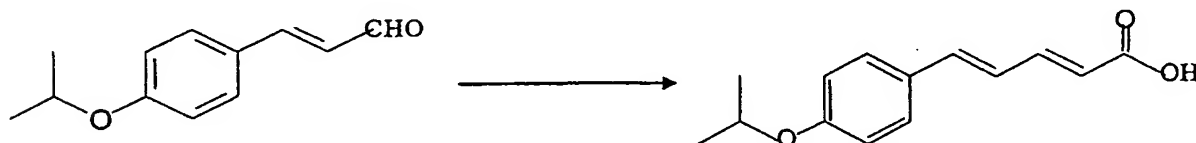
saturated aqueous solution of ammonium chloride (10 ml), followed by dilution with water (100 ml), separating the organic layer and extracting the aqueous layer with solvent ether (2x100 ml). The combined organic layer is washed with water (2x20 ml), dried over anhydrous sodium sulphate and concentrated in vacuo to yield 1-(4-isopropoxyphenyl) ethanol, in a semisolid of general formula 4 in 92.5% yield.

(ii) Preparation of 3-(4-isopropoxyphenyl)- 2E - propenal of formula 3, (R = C₃H₇)



A solution of 1-(4-isopropoxyphenyl) ethanol of formula 4 (4.8g, 27 mmol) in dimethyl formamide (10 ml) is slowly added to phosphorus oxychloride (8 ml) in DMF (12 ml) with stirring at 0°C. The reaction mixture is stirred for 2 hours then allowed attaining room temperature followed by heating on an oil bath for 36 hour at 40°C. After the completion of the reaction as monitored by TLC, contents of the reaction mixture are poured into ice cold water (500 ml), neutralised with dilute alkali solution and saturated by adding sodium chloride. The aqueous portion is extracted with ethyl acetate (3x100 ml), organic layer washed with water, dried over anhydrous sodium sulphate and stripped off the solvent under vacuum to furnish crude product (4.8g). It was purified by column chromatography over silica gel to yield a semisolid 3-(4-isopropoxyphenyl) - 2E - propenal of formula 3 (80%).

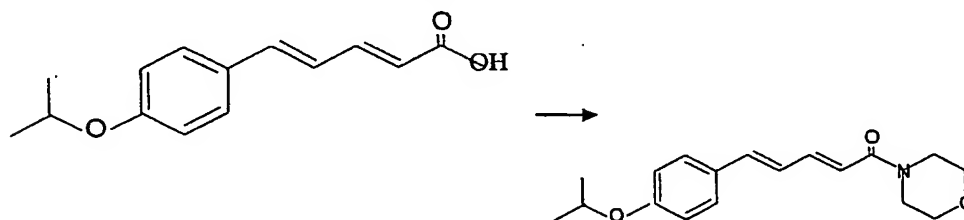
(iii) Preparation of 5-(4-isopropoxyphenyl)-2E, 4E-pentadienoic acid of formula 2_n (n=2 and R = C₃H₇)



A mixture of triphenyl phosphine (4.7g, 18 mmol) and ethyl bromoacetate (20 ml, 18 mmol) in anhydrous dimethoxy ethane is refluxed for 2 hour and to the intermediate thus formed is added 3-(4-isopropoxyphenyl)- 2E- propenal of formula 3 (2.5g, 13mmol), sodium hydride (0.5g) in small proportions. The reaction mixture is continuously stirred for 72 hour at 60°C. The reaction mixture is then worked up by pouring onto ice cold water and

extraction with dichloromethane (3x100 ml). The organic layer washed with water, dried over anhydrous calcium chloride and concentrated into vacuum. The crude 5-(4-isopropoxyphenyl)-2E, 4E-pentadienoate obtained above is hydrolysed directly without purification in 10% methanolic potassium hydroxide solution on a water bath for 6 hour. On cooling, the contents diluted with water (200 ml) and extracted with dichloromethane (2x40ml), the extracted aqueous portion is acidified with 2N hydrochloric acid solution. The resulting precipitate is filtered, washed with water and air dried to furnish crude acid (2.40g, 80%). Crystallisation of the crude acid from ethyl acetate: benzene (19:1) furnished pure 5-(4-isopropoxyphenyl)-2E, 4E-pentadienoic acid of formula 2, m p 180°C.

(iv) Preparation of 5 - (4 - isopropoxy phenyl) - 2E, 4E-pentadienoic acid morpholine amide of formula 1 (n=2, x =O and R = C₃H₇)



Freshly distilled thionyl chloride (0.5 ml) is added to a solution of 5-(4 isopropoxyphenyl)-2E, 4E-pentadienoic acid (1.4g, 6mmol) of formula 2 in dry dichloromethane and mixture is refluxed on a water bath for 1 hour. Solvent is removed from the acid chloride in vacuo along with excess of thionyl chloride. A solution of morpholine (0.6 ml, 7mmol) in dichloromethane is added to the acid chloride prepared above and mixture stirred for 1 hour. After completion of the reaction, the organic layer is made free of excess of morpholine using dilute hydrochloric acid solution. The organic layer is washed with water, dried and concentrated under vacuum to furnish crude product (1.7g, 94%), purified by crystallisation from ethyl acetate: hexane (9:1) to yield 5-(4 - isopropoxy phenyl)-2E, 4E-pentadienoic acid morpholine amide of formula 1.

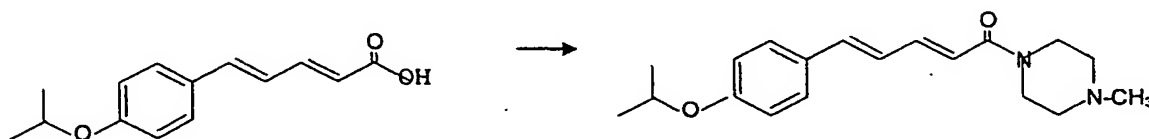
Pale yellow crystals m.p. 134°C, analysed for C₁₈H₂₃NO₃

¹H NMR (200 M Hz) CDCl₃ : δ 1.35 (6H, d, J=6Hz, -(CH₃)₂ -CH), 3.65 (8H, bs, N-(CH₂)₂-(CH₂)₂O-), 4.60 (1H, h, J=6Hz, -OCH(CH₃)₂), 6.40 (1H, d, J=14.0Hz, COCH=CH-), 6.65 -7.05 and 7.20- 7.85 (7H, 2x bs, Ar-H and olefinic H).

MS (E I): M⁺ - 1 at m/z 300 (35.6), 258 (11.1), 215 (18.5), 173 (100), 145 (18.2), 114 (24.0), 86 (22.6) and 70 (25.3).

Example-2

Preparation of 5-(4-isopropoxy phenyl)-2E,4E-pentadienoic acid N-methyl piperazine amide of formula 1 ($n=2$, $x=N-CH_3$ and $R=C_3H_7$)



5

To a solution of 5-(4-isopropoxy phenyl)-2E, 4E-pentadienoic acid (0.93g, 4mmol) of formula 2 prepared by the method as described in example 1 (i-iii) in dry dichloromethane (40 ml) is added freshly distilled thionyl chloride (0.3ml) and the mixture is refluxed on a water bath for 1 hr. thereafter the contents concentrated in vacuo and redissolved in dichloromethane (10ml). A solution of N-methyl piperazine (0.4 ml, 4mmol, in dichloromethane is added to acid chloride solution and the mixture is stirred for 2 hr at room temp. After the completion of the reaction, the contents are taken up in water (50ml), the organic layer separated and the aqueous layer extracted with dichloromethane (2x15ml). The combined organic layer is concentrated and the crude product purified by column chromatography on alumina (neutral) using chloroform: methanol (9:1) as eluent to give product, a semisolid (1.1g, yield 93%), analysed for $C_{19}H_{26}N_2O_2$.

1H NMR(200MHz) $CDCl_3$ δ 1.31 (6H, d, $J=6.05$ Hz, $(CH_3)_2-C$) 2.31 (3H, s, $-N-CH_3$), 2.50 (4H, t, $J=5.06$, $-N-(CH_2)_2$), 3.71 (4H, m, $-N-(CH_2)_2$), 4.57 (1H, h, $J=6.0$ Hz, $OCH-CH_3$), 6.67 (1H, d, $J=15.3$ Hz: $CH=CH-CO$), 6.85 (2H, d $J=8.7$ Hz, $2 \times Ar-H$), 6.79-6.88 (1H, m, olefinic $-H$), 7.23-7.38 (1H, m olefinic $-H$), 7.44 (2H, d, $J=8.7$ Hz, $2 \times Ar-H$) and 7.76 (1H, d, $J=15.3$ Hz, $CH=CH-CO$).

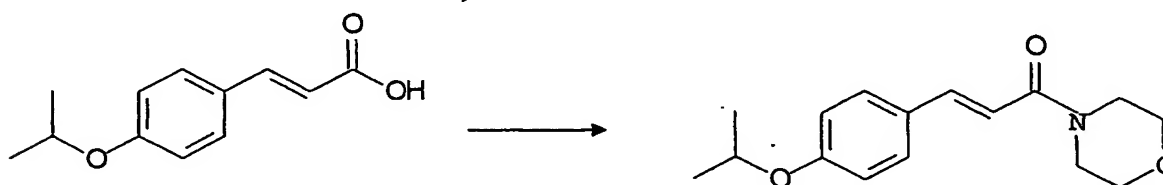
MS (EI): M^+-1 at m/z 313(16.9), 214(10.8), 170(12.6), 144(31.8), 118(21.9), 70(74.3) and 57(100).

25

Example-3

Preparation of 3-(4-isopropoxy phenyl) -2E-propenoic acid morpholine amide of formula 1 ($n=1$, $x=O$ and $R=C_3H_7$)

30



3-(4-isopropoxy phenyl)-2E-propenoic acid of formula 2, $n=1$ and $R = C_3H_7$, (2.06, 10mmol) a known compound in the art of synthesis is reacted with freshly distilled thionyl chloride (1.0ml) in dry dichloromethane (15ml) on a water bath for 1 hr. Solvent is removed in vacuo from the intermediate acid chloride along with the excess of thionyl chloride. A solution of morpholine (0.90ml) in dry dichloromethane is added to the acid chloride prepared above and mixture stirred for 1 hr at room temp. After the completion of the reaction the organic layer is made free of excess of morpholine using dilute hydrochloric acid solution. The organic layer is washed with water, dried and concentrated under vacuum to furnish crude product which on crystallisation from ethyl acetate: hexane, furnished 3-(4-isopropoxy phenyl)-2E-propenoic acid morpholine amide of general formula 2 where $n=1$, (m.p $98^{\circ}C$, Yield 2.66g, 97%).

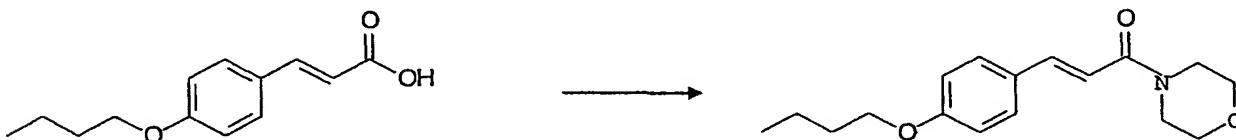
Creamish crystals m.p. $98^{\circ}C$, analysed for $C_{16}H_{21}NO_3$

1H NMR (200MHz) $CDCl_3$: δ 1.30 (6H, d, $J=6Hz$, $-(CH_3)_2-C$), 3.70 (8H, s, $O(CH_2)_2-(CH_2)_2-N$), 4.55 (1H, h, $J=6Hz$, $OCH-(CH_3)_2$), 6.65 (1H, d, $J=15.3Hz$, $COCH=CH-$), 6.85 (2H, d, $J=8.5Hz$, 2xAr-H), 7.40 (2H, d, $J=8.5Hz$, 2xAr-H) and 7.65 (1H, d, $J=15.3Hz$, $COCH=CH$).

MS (EI): M^+ at m/z 275 (28.8), 233 (12.7), 189 (34.6), 164 (14.1), 147 (100), 119 (30.7) and 91 (24.9).

Example-4

Preparation of 3-(4-butyloxy phenyl) -2E-propenoic acid morpholine amide of formula 1 ($n=1$, $x=O$ and $R = C_4H_9$)



25

To a solution of 3-(4-butyloxyphenyl) -2E-propenoic acid (2.2g, 10 mmol) in dichloromethane (40ml) is added thionyl chloride (0.8ml) and the resulting acid chloride made to react with morpholine (0.9ml) as per procedure described in example 3 to give a solid (2.7g, 90%) which is purified by crystallisation from ethyl acetate: n-hexane (9:1), mp $117^{\circ}C$, analysed for $C_{17}H_{23}NO_3$.

30

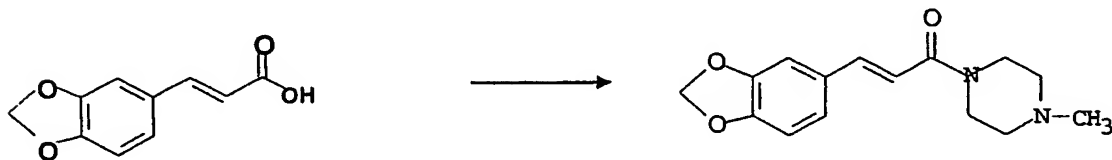
1H NMR (200MHz) $CDCl_3$: δ 1.0 (3H, t, $J=6.5Hz$ - CH_2-CH_3), 1.7 (2H, m, $-CH_2-CH_2-CH_3$) 1.8 (2H, m, $-OCH_2-CH_2-CH_2-$), 3.76 (8H, bs, 2x $-N(CH_2)_2-(CH_2)_2-O-$), 4.03 (2H, t, $J=6.5Hz$, $-OCH_2-CH_2-$), 6.75, (1H, d, $J=15Hz$, $-CH=CH-CO$), 6.96 (2H, d, $J=8Hz$, 2xAr-H), 7.53

(2H, d, J = 8 Hz, 2xAr-H) & 7.78 (1H, d, J = 15Hz, -CH=CH-CO).

MS(EI):M⁺-1 at m/z 288(28.5), 203 (91), 146(100), 118(52), 101(13) & 86(9.7).

Example-5

- Preparation of 3-(3,4-methylenedioxy phenyl) -2E-propenoic acid N-methyl piperazine
5 amide of formula 1 (n=1, x=N-CH₃ and Ar = 3', 4'- methylenedioxy phenyl.)



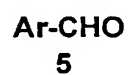
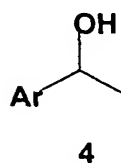
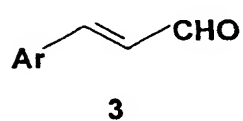
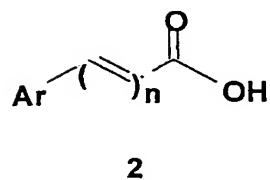
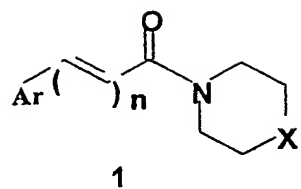
- 10 The N-methyl piperazine amide of 3-(3,4-methylenedioxy phenyl) -2E-propenoic acid is prepared from 3-(3,4-methylenedioxy phenyl) -2E-propenoic acid (1.92g, 10mmol), thionyl chloride (0.8ml) and N-methyl piperazine (1.0ml,10mmol) by the method described for example 2 to give solid (2.55g, 91%), purified by crystallisation from chloroform: methanol (9:1), m.p 84°C, analysed for C₁₅H₁₈N₂O₃.

- 15 ¹HNMR(200 Hz) CDCl₃, δ 2.33 (3H, s, -N-CH₃), 2.45 (4H, t, J= 5.05Hz, -N-(CH₂)₂), 3.72 (4H, t, J= 5.05 Hz, N-(CH₂)₂), 6.03 (2H, s, -OCH₂O-), 6.72 (1H, d, J= 15.0Hz, CH=CH-CO), 6.82 (1H, d, J= 8.5Hz, Ar-H), 6.95-7.23 (2H, m, 2xAr-H) and 7.65 (1H, d, J= 15.0Hz, CH=CH-CO).

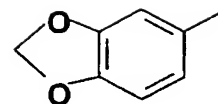
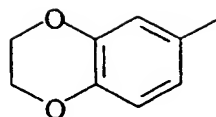
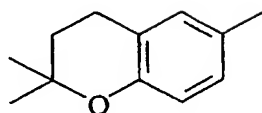
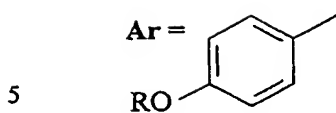
MS(EI):M⁺ at m/z 274(22.2) 174(17.7), 143(13.8), 115(13.2), 70(100) and 57(83.3).

- 20 The main advantages of the present invention are:

- 1 The present invention provides novel substituted aryl alkenoic acid heterocyclic amides of general formula 1
2. Novel compounds with hot, pungent and spicy properties and synthetic substitutes
25 for natural compounds and their process of preparation.
3. Novel compounds provided can be used as food additives.
4. The compounds in the present invention provides the pungency index in the range of 10³ to 10⁷ units as compared to the known pungent substances which have pungency index in the range of 10³ to 10⁶ units.
- 30 5. Novel compounds which may also be useful in the study of bioavailability enhancers and hepatic drug metabolism.
6. Novel compounds which may be useful as new test models in the development of anti-inflammatory and anti-arthritis drugs.



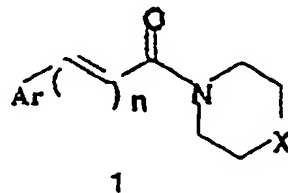
X=O,-N-CH₃
n=1 or 2



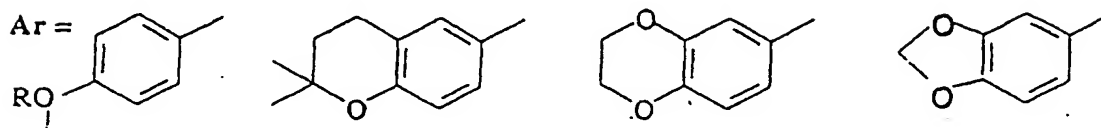
R= CH₃, C₂H₅, C₃H₇, C₄H₉, C₅H₁₁

Claims

1. Novel arylalkenoic acid heterocyclic amide of general formula (I) useful as food additives and in pharmaceutical applications,



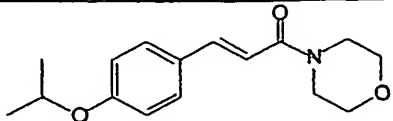
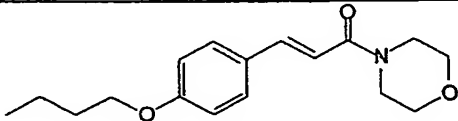
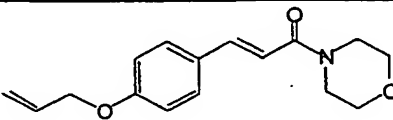
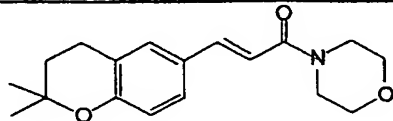
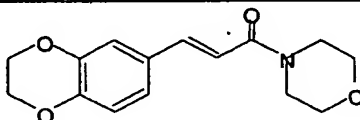
Wherein $n = 1$ or 2 , $X = O$ or $N-CH_3$ and



wherein $R =$ linear or branched C_1 to C_5 alkyl chain

2. Arylalkenoic acid heterocyclic amide compounds as claimed in claim 1 wherein the preferred compound having structure and names as given below:

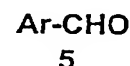
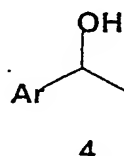
S.No	Structure	M.F.	M.P.°C	Pungency index
i		$C_{16}H_{19}NO_3$	133	10^6
ii		$C_{18}H_{23}NO_3$	134	10^7
iii		$C_{20}H_{25}NO_3$	171	10^4
iv		$C_{17}H_{19}NO_4$	137	10^4
v		$C_{14}H_{17}NO_3$	95	10^5

vi		$C_{16}H_{21}NO_3$	98	10^6
vii		$C_{18}H_{23}NO_3$	117	10^7
viii		$C_{17}H_{23}NO_3$	70	10^4
ix		$C_{16}H_{19}NO_3$	88	10^6
x		$C_{15}H_{17}NO_4$	139	10^4

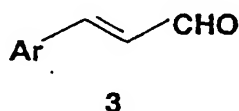
Compound No.	Compound Name
i)	5- (4 –methoxy phenyl) – 2E, 4E-pentadienoic acid morpholine amide
ii)	5- (4 – isopropoxy phenyl) - 2E, 4E-pentadienoic acid morpholine amide
iii)	5- (2H)-2,2-dimethyl-3,4-dihydro-benzopyran-6yl-2E, 4E-pentadienoic acid morpholine amide
iv)	5- (3,4 –ethylenedioxy phenyl) - 2E, 4E-pentadienoic acid morpholine amide
v)	3-(4 –methoxy phenyl)-2E-propenoic acid morpholine amide
vi)	3-(4 –isopropoxy phenyl)-2E- propenoic acid morpholine amide
vii)	3-(4 –butyloxy phenyl)-2E- propenoic acid morpholine amide
viii)	3-(4 –allyloxy phenyl)-2E- propenoic acid morpholine amide
ix)	3-[(2H)-2,2-dimethyl-3,4-dihydro-benzopyran-6yl]-2E-propenoic acid morpholine amide
x)	3 - (3,4 –ethylenedioxy phenyl) – 2E-propenoic acid morpholine amide

- 5 3. Compounds as claimed in claims 1 and 2 are useful as thermogenic, pungent, spicy agents and constitute as food additives.
4. Compounds as claimed in claims 1 and 2 can be used as best models for the study and management phenomenon of ailments like pain and inflammation.

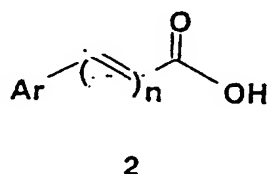
5. Compounds as claimed in claim 4, wherein the pathological conditions for the ailment may be selected from arthritis, spinal cord injury or diabetic neurotherapy.
6. Compounds as claimed in claims 1 and 2 can be used as best models for the development of inflammatory drugs, bioavailability enhances and also, for the study of hepatic drug metabolic mechanism.
7. A process for the preparation of aryl alkenoic acid heterocyclic amides as claimed in claim 1, the said process comprising steps of:
- (a) reacting aldehyde of general formula (5) with alkyl magnesium halide with constant stirring at an ambient temperature in an anhydrous ethereal solvent to produce corresponding phenyl ethanol of general formula (4),



- (b) treating the compound of general formula (4) with dimethyl formamide and phosphorous oxychloride at 0° to 10°C for 20-40 hours, working up the reaction mixture by adjusting the pH of the solution and isolating the product of general formula (3) by using conventional method,



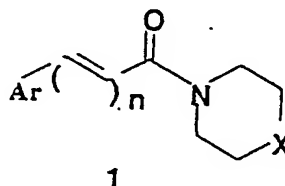
- (c) reacting the compound of general formula (3) with witting reagent in presence of a base at a temperature range of 15-80°C in an ethereal solvent for a period of 1-80 hours to get the corresponding carboxylic ester.
- (d) hydrolysing the ester of step (c) with strong alkali solution followed by acidification of the reaction mixture to produce the corresponding carboxylic acid of general formula (2),



(e) reacting compound of step (d) of general formula (2) with thionyl chloride in presence of an organic solvent at a temperature in the range of reflux temperature of 70°C-80°C, removing the solvent to obtain the corresponding acid chloride,

5 (f) reacting the acid chloride of step (e) with heterocyclic amine in an inert organic solvent at a temperature in the range of 0 to 50°C for 1 to 16 hours, isolating the product by purifying the reaction mixture to obtain product of formula (I).

10



15 8. A process as claimed in claim 7, wherein in step (a) the alkyl magnesium halide used is methyl magnesium iodide.

9. A process as claimed in claim 7, wherein in step (a) the ethereal solvent used is selected from the group consisting of diethyl ether and tetrahydrofuran and preferably tetrahydrofuran.

20 10. A process as claimed in claim 7, wherein in step (b) the solution of the reaction mixture is adjusted to pH 6 to 8.

11. A process as claimed in claim 7, wherein in step (b) the product after pre adjustment is isolated by either filtration or extraction with an organic solvent selected from the group consisting of ethylacetate, chloroform, dichloromethane and dichloroethane, preferably ethylacetate.

25

12. A process as claimed in claim 7, wherein in step (c), the witting reagent used is prepared from the reaction of equimolar mixture of triphenyl phosphine and bromomethyl acetate or bromoethylacetate and preferably bromoethylacetate.

13. A process as claimed in claim 7, wherein in step (c) the base used is selected from a group consisting of sodium hydride, sodium methoxide and sodium ethoxide and preferably sodium hydride.

30

14. A process as claimed in claim 7, wherein in step (c) the ethereal solvent used is selected from a group consisting of diethylether, dimethoxyethane, tetrahydrofuran, chloroform, and dichloromethane and preferably dichloromethane.

15. A process as claimed in claim 7, wherein in step (d) the alkali used for hydrolysis is selected from a group consisting of sodium hydroxide, potassium hydroxide and calcium hydroxide and most preferably sodium hydroxide.
16. A process as claimed in claim 7, wherein in step (d) the acidification is performed
5 using sulfuric acid or hydrochloric acid and preferably hydrochloric acid.
17. A process as claimed in claim 7, wherein in step (e) the organic solvent used for extraction is selected from a group consisting of dichloromethane, benzene, diethylether and toluene preferably dichloromethane.
18. A process as claimed in claim 7, wherein in step (f) the organic solvent used is
10 selected from a group consisting of benzene, toluene, dichloromethane and ethyl acetate and preferably dichloromethane.
19. A process as claimed in claim 7, wherein in step (f) the purification of the product is carried out by employing crystallization or column chromatography technique.

INTERNATIONAL SEARCH REPORT

PCT/IB 02/00507

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D295/185 C07D311/58 C07D319/18 A61K31/5375 A23L1/226

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, CHEM ABS Data, EPO-Internal, BEILSTEIN Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 002 735 A (HAARMANN UND REIMER G.M.B.H., FED. REP. GER.) 11 July 1979 (1979-07-11) abstract page 13; example 4; tables claims	1-18
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. brn806917 XP002207115 abstract & PUSCARU ET AL: FARMACIA, vol. 9, 1961, pages 345-347, Bucharest	1-18



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

S document member of the same patent family

Date of the actual completion of the international search

23 July 2002

Date of mailing of the international search report

12/08/2002

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

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Stix-Malaun, E

INTERNATIONAL SEARCH REPORT

PCT/IB 02/00507

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>KOUL, SURRENDER ET AL: "Structure-activity relationship of piperine and its synthetic analogs for their inhibitory potentials of rat hepatic microsomal constitutive and inducible cytochrome P450 activities" BIOORGANIC & MEDICINAL CHEMISTRY (2000), 8(1), 251-268 , XP002207113 page 253; example 10; table 1</p>	1-18
X	<p>CHEMICAL ABSTRACTS, vol. 107, no. 5, 3 August 1987 (1987-08-03) Columbus, Ohio, US; abstract no. 39671, DO, GYONG SAM ET AL: "Syntheses and central nervous depressant activities of piperidine derivatives (V). Methylenedioxyphenyl alkenoic acid amides" XP002207114 abstract & YAKHAK HOECHI (1986), 30(4), 163-8 ,</p>	1-18
X	<p>US 6 008 376 A (SHARPLESS K BARRY ET AL) 28 December 1999 (1999-12-28) Figure 2 example 7</p>	1-18
X	<p>DATABASE CHEMCATS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002207116 Order numbers: 6650845, 6492099 & "CHEMBRIDGE PRODUCT LIST" 17 January 2002 (2002-01-17) , CHEMBRIDGE CORPORATION , 16981 VIA TAZON, SUITE G, SAN DIEGO, CA, 92127 USA</p>	1-18
A	<p>RAGHVENDRA C K A ET AL: "BIOCHEMICAL BASIS OF ENHANCED DRUG BIOAVAILABILITY BY PIPERINE: EVIDENCE THAT PIPERINE IS A POTENT INHIBITOR OF DRUG METABOLISM" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AMERICAN SOCIETY FOR PHARMACOLOGY AND, US, vol. 232, no. 1, 1985, pages 258-262, XP000885920 ISSN: 0022-3565 cited in the application abstract Figure 1 page 259, column 1</p>	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/IB 02/00507

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0002735	A	11-07-1979	DE 2757506 B1	13-06-1979
			DE 2860322 D1	19-02-1981
			EP 0002735 A2	11-07-1979
			JP 1356051 C	24-12-1986
			JP 54098764 A	03-08-1979
			JP 61021475 B	27-05-1986
			US 4209446 A	24-06-1980
US 6008376	A	28-12-1999	NONE	